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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/828,395	04/19/2004	John K. Jackson	UBC.P-032	5836

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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/828,395	JACKSON ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *4,5,9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/8/05, 3/17/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group I, claims 2, 3, 7 and 8, linking claims 1 and 6, and SEQ ID NO: 5 in the reply filed on July 19, 2005 is acknowledged.

Claims 4, 5, 9 and 10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on October 27, 2005.

Claims 1-3 and 6-8 are examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Each of these claims is indefinite because they refer to a method having multiple steps (the method comprises "the steps of") but then recite only a single step.

Claims 6-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 recites the limitation "the cells of the cancer" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claims 7 and 8 are indefinite for the same reason due to their dependence on claim 6.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1 and 6 are directed to methods of treating a non-cancerous angiogenesis related disease or reducing angiogenesis by reducing the effective amount of clusterin. In claim 6 the method is carried out by treating cancerous cells. These claims encompass treatment of any non-cancerous disease that exhibits angiogenesis as a symptom of the disease and also encompasses use of a large genus of compounds that might be used to perform such a treatment.

The compounds encompassed by the instant claims include nucleic acid inhibitors such as antisense oligonucleotides, ribozymes, aptamers and siRNAs, peptide

and antibody inhibitors, small organic molecules and inorganic molecules that would function to inhibit expression of clusterin from any species.

The specification discloses several antisense oligonucleotides and several siRNAs targeted to human clusterin. The specification discloses that one antisense compound decreases the viability of cultured HUVEC cells and that the response is greater in the presence of one of three anticancer drugs. The specification fails to disclose the treatment of any disease or disorder by reduction of clusterin expression in any organism using any inhibitor, known or unknown. The specification does not describe treatment of cancer in order to reduce angiogenesis of a non-cancerous angiogenesis related disease. The specification also does not describe the structure of any other inhibitors that correspond to the function of inhibiting human clusterin nor does it describe the structure of any inhibitor that has the function of reducing clusterin from any species other than human. Clusterin is a gene widely expressed across species, but the essential motifs and domains of clusterin have not been sufficiently well-characterized that one of skill in the art would immediately recognize what compounds would be inhibitors of any particular homologue of clusterin and would have the function of treating a non-cancerous angiogenesis related disease.

In order for the written description provision of 35 USC 112, first paragraph to be satisfied, applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed. For example, MPEP 2163 states in part,

"An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

The skilled artisan cannot envision treatment of a non-cancerous angiogenesis-related disease using an inhibitor of clusterin. Nor can the skilled artisan envision the detailed structure of the full genus of encompassed inhibitors of clusterin from any species, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Therefore, while the specification provides adequate description of the antisense oligonucleotides and siRNAs targeted to human clusterin, the full breadth of non-nucleic acid inhibitors of human clusterin and inhibitors of any type directed to clusterin of any species other than human encompassed by the claims and the claimed methods of treating a non-cancerous angiogenesis-related disease by inhibiting expression of clusterin do not meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Claims 1-3 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reduction of clusterin expression by

administration of an antisense oligonucleotide targeted to clusterin in cells *in vitro*, does not reasonably provide enablement for treatment of a non-cancerous angiogenesis-related disease by administration of an antisense oligonucleotide targeted to clusterin in any organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Claims 1 and 6 are directed to treatment or reduction in angiogenesis of a non-cancerous angiogenesis-related disease by administering a therapeutic composition that reduces the effective amount of clusterin. Claims 2, 3, 7 and 8 limit one of claims 1 or 6 by limiting the therapeutic composition to an antisense oligonucleotide that may be SEQ ID NO: 5.

The specification provides general guidance with regard to formulations and routes of administration of antisense oligonucleotides. The specification also describes that administration of SEQ ID NO: 5 to HUVEC cells in culture reduces clusterin levels. The specification does not describe administration of antisense oligonucleotides

directed to clusterin to any organism for the purpose of reducing angiogenesis in any type of cell.

The state of the prior art is such that inhibition of gene expression *in vitro* is routine, but *in vivo* inhibition of gene expression at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration.

The problems of nucleic acid based therapies and antisense technology are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 2000, vol. 6, p 72-81), Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol 1, p. 503-514) and Jen et al. (Stem Cells 2000, vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

Jen et al. state (see page 313, second column, second paragraph)

> "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol 1, p. 503-514) state on page 511

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of gene expression, as claimed. The specification provides an example of reduction of viability of HUVEC cells using an antisense oligonucleotide targeted to clusterin, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states

> "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide."

Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. One of skill in the art would not know how to deliver oligonucleotides to an organism in such a way that would ensure an amount sufficient to modify or inhibit expression of a target gene is delivered to the proper cell.

In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of inhibiting gene expression using nucleic acids *in vivo* are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, reducing angiogenesis in a non-cancerous angiogenesis-related disease.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using antisense oligonucleotides in therapeutic applications in any organism. The field of antisense therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of reducing angiogenesis or treating a non-cancerous angiogenesis related disease in any organism as the art of inhibiting gene expression by introducing antisense oligonucleotides into an organism is neither routine nor predictable. In order to practice the claimed invention *in vivo* in all organisms a number of variables would have to be optimized, including 1). the mode of delivery of the antisense oligonucleotide to an organism that would allow it to reach the targeted cell, 2). the amount of antisense oligonucleotide that would need to be delivered in order to bind a sufficient amount of clusterin to reduce angiogenesis once it reached the proper cell and 3). ensuring the antisense oligonucleotide remains viable in a cell for a period of time that allows reduction of angiogenesis to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each antisense oligonucleotide. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation required becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1-3 and 6-8 are not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 6 and 7 are rejected under 35 U.S.C. 102(b) as anticipated by Monia et al. (US 6,383,808).

Claim 6 is directed to a method of reducing angiogenesis in a non-cancerous angiogenesis-related disease by administering a composition that reduces the amount of clusterin. Claim 7 limits the method to use of inhibitors that are antisense oligonucleotides complementary to SEQ ID NO: 1.

Monia et al. disclose and claim (see claim 13) a method of inhibiting expression of human clusterin by administering to a cell *in vitro* an antisense oligonucleotide. One of these antisense oligonucleotides is designated as SEQ ID NO: 18, which is complementary to nucleotides 101-120 of instant SEQ ID NO: 1. The method of Monia et al. is not specifically disclosed as reducing angiogenesis but since it shares the active step of the instantly claimed method it would perform this function absent evidence to the contrary.

Thus, Monia et al. disclose all limitations of and anticipate claims 6 and 7.

Claims 6-8 are rejected under 35 U.S.C. 102(b) as anticipated by Gleave et al. (WO 00/49937).

Claim 6 is directed to methods of reducing angiogenesis in a non-cancerous angiogenesis-related disease by administering a therapeutic composition effective to reduce the amount of clusterin. Claim 7 limits the method to use of inhibitors that are antisense oligonucleotides. Claim 8 limits the method to use of SEQ ID NO: 5.

Gleave et al. disclose and claim (see claims 6, 7 and 9) a method of treating prostate cancer comprising administering a composition that inhibits expression of TRPM-2, another name for clusterin. This composition may be an antisense oligonucleotide and may have the sequence shown as SEQ ID NO: 4, which is identical to SEQ ID NO: 5 of the instant application. The method of Gleave et al. is not specifically disclosed as reducing angiogenesis but since it shares the active step of the instantly claimed method it would perform this function absent evidence to the contrary.

Thus, Gleave et al. disclose all limitations of and anticipate claims 6-8.

Claims 6-8 are rejected under 35 U.S.C. 102(e) as anticipated by Gleave et al. (US 6,900,187).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim 6 is directed to methods of reducing angiogenesis in a non-cancerous angiogenesis-related disease by administering a therapeutic composition effective to reduce the amount of clusterin. Claim 7 limits the method to use of inhibitors that are antisense oligonucleotides. Claim 8 limits the method to use of SEQ ID NO: 5.

Gleave et al. disclose and claim (see claim 3) a method of treating prostate cancer in an individual that comprises administration of an antisense oligonucleotide having a particular sequence that inhibits expression of TRPM-2 another name for clusterin. The sequence of Gleave et al., SEQ ID NO: 4, is identical to that of SEQ ID NO: 5 of the instant application. The method of Gleave et al. is not specifically disclosed as reducing angiogenesis but since it shares the active step of the instantly claimed method it would perform this function absent evidence to the contrary.

Thus, Gleave et al. disclose all limitations of and anticipate claims 6-8.

Claims 6-8 are rejected under 35 U.S.C. 102(e) as anticipated by Gleave et al. (US 2003/0158130).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim 6 is directed to methods of reducing angiogenesis in a non-cancerous angiogenesis-related disease by administering a therapeutic composition effective to reduce the amount of clusterin. Claim 7 limits the method to use of inhibitors that are antisense oligonucleotides. Claim 8 limits the method to use of SEQ ID NO: 5.

Gleave et al. discloses and claims (see currently pending claims 36-39 and 42) a method of treating cancer that comprises administration of a composition that inhibits expression of TRPM-2, another name for clusterin. Gleave et al. also disclose that the composition may be an antisense oligonucleotide having the sequence shown as SEQ ID NO: 4, which is identical to the SEQ ID NO: 5 of the instant application. The method of Gleave et al. is not specifically disclosed as reducing angiogenesis but since it shares the active step of the instantly claimed method it would perform this function absent evidence to the contrary.

Thus, Gleave et al. disclose all limitations of and anticipate claims 6-8.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0760811. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
December 16, 2005

J.D. SCHULTZ, Ph.D.
PATENT EXAMINER